

Rifabutin

Brand Name: Mycobutin

Drug Class: Opportunistic Infection and Other Drugs



Drug Description

Rifabutin is a semisynthetic ansamycin antibiotic derived from rifamycin S. It is structurally related to rifampin and is similar to rifampin in many of its properties, including its spectrum of activity against gram-negative and gram-positive organisms. [1]

HIV/AIDS-Related Uses

Rifabutin was approved by the FDA on August 23, 1996, for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection.[2] [3] Rifabutin is also used alone or in combination with azithromycin for the prevention of disseminated MAC disease in AIDS patients.[4]

Rifabutin is used as an alternative to rifampin in multiple-drug regimens for the treatment of tuberculosis (TB) in HIV infected patients who are taking certain antiretroviral drugs. A rifabutin-containing regimen has less potential for interaction with antiretrovirals, potentially better absorption in patients with advanced HIV, and greater tolerability in patients with rifampin-induced hepatotoxicity.[5] Rifabutin is currently being investigated to determine its optimal dosing schedule when administered concurrently with the antiretroviral drug zidovudine.[6]

Rifabutin is also used alone or in combination with other drugs to prevent the development of clinical TB or for the treatment of latent TB infection in HIV infected patients.[7]

Non-HIV/AIDS-Related Uses

Rifabutin is designated an orphan drug by the FDA for the treatment of disseminated MAC disease.[8] It is also used as an alternative to rifampin in multiple-drug regimens for the prevention and treatment of pulmonary tuberculosis.[9]

Pharmacology

Rifabutin inhibits DNA-dependent RNA polymerase and subsequent initiation of

transcription, thereby inhibiting protein synthesis. Rifabutin is active against mycobacteria, gram-positive and gram-negative bacteria, *Chlamydia trachomatis*, and *Toxoplasma gondii*. [10]

Rifabutin is readily absorbed from the gastrointestinal (GI) tract, and mean peak plasma levels of 375 ng/ml are reached within an average of 3.3 hours. Taking rifabutin capsules with high-fat meals slows the rate of absorption but does not affect the extent of absorption. In one study, the mean absolute bioavailability of rifabutin averaged 20% in five HIV infected patients who received both oral and IV doses. Pharmacokinetic dose-proportionality was established in early symptomatic HIV infected patients over a dose range of 300 to 900 mg. Total recovery of radioactivity in the urine indicates that at least 53% of an orally administered dose is absorbed from the GI tract.[11]

Rifabutin is highly lipophilic and is widely distributed with increased intracellular tissue uptake. In five HIV infected patients given an IV dose of rifabutin, estimates of apparent steady state distribution volume exceeded total body water by 15-fold. Intracellular tissue levels are substantially higher than plasma concentrations. The lung-to-plasma concentration ratio at 12 hours was found to be approximately 6.5 in four surgical patients administered an oral dose.[12] Rifabutin crosses the blood-brain barrier; cerebrospinal fluid concentrations are approximately 50% of the corresponding serum concentrations.[13]

Rifabutin is in FDA Pregnancy Category B. No adequate or well-controlled studies have been done in humans; however, in laboratory animals, fetal abnormalities occurred after the animals were given doses of rifabutin that greatly exceeded the recommended human dose. It is not known whether rifabutin is distributed into human milk; however, the possibility of adverse effects to the nursing infant from rifabutin should be considered in determining whether to discontinue nursing or treatment with rifabutin.[14]

About 85% of rifabutin is bound to plasma

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Pharmacology (cont.)

proteins. Binding does not appear to be influenced by renal or hepatic dysfunction.[15] Rifabutin undergoes hepatic biotransformation to five known metabolites. The 25-O-desacetyl metabolite has activity equal to the parent drug and contributes up to 10% of the total antimicrobial activity. In a study of seven healthy adults, rifabutin was eliminated slowly from plasma, with a mean terminal half-life of 45 hours. Systemic levels of rifabutin following multiple dosing decreased by 38%; however, terminal half-life did not change, presumably reflecting distribution-limited elimination. Renal and biliary clearance of rifabutin as unchanged drug each contribute about 5% to mean systemic clearance. About 30% of a dose is eliminated in feces. In a study of three healthy adults, 53% of a radiolabeled oral dose was excreted in urine, primarily as metabolites.[16]

In clinical trials, patients with severe renal impairment (defined as creatinine clearance less than 30 ml/min) given oral rifabutin had a 71% increase in the area under the concentration-time curve (AUC) over that of individuals with no renal impairment. Patients with moderate renal impairment had an AUC increase of 41%. The manufacturer suggests dosage reduction in severely impaired patients.[17]

Adverse Events/Toxicity

The most common adverse effects of rifabutin requiring medical attention are allergic reactions, including skin rash and itching; GI effects, including anorexia, diarrhea, dyspepsia, nausea, and vomiting; and hematologic abnormalities, including anemia, leukopenia, neutropenia, and thrombocytopenia. In clinical trials, only the incidence of neutropenia was significantly greater with rifabutin than with placebo; however, rifabutin has been clearly linked to thrombocytopenia in rare cases.[18] [19]

Uveitis, characterized by pain, redness, and possible temporary or permanent loss of vision, may occur with rifabutin use.[20] The risk of uveitis appears to be greatest in patients taking higher doses of rifabutin in combination with macrolide antibiotics or fluconazole. Patients who

developed uveitis had mild to severe symptoms that resolved after treatment with corticosteroids and/or mydriatic eye drops, although resolution of symptoms occurred after several weeks in some patients.[21]

Less serious adverse effects include abdominal pain and bloating, chest pain, taste perversion, headache, and insomnia. In addition, rifabutin may discolor body fluids, giving a red-orange or red-brown color to urine, feces, saliva, skin, sweat, and tears. Discolored tears may stain soft contact lenses permanently.[22]

Drug and Food Interactions

Rifabutin generally can be administered without regard to meals.[23]

Rifabutin, like other rifamycins, can induce the hepatic microsomal cytochrome P450 (CYP) oxidase system, causing interactions with drugs that are metabolized by these enzymes, including itraconazole and clarithromycin. Rifabutin appears to induce hepatic microsomal enzymes to a lesser degree than rifampin; however, rifabutin's structural similarity to rifampin may cause reduced activity of drugs that are affected by rifampin.[24]

By inducing CYP oxidases, rifabutin may accelerate the metabolism of some HIV protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir) and nonnucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, and nevirapine); these antiretrovirals may, in turn, slow the metabolism of rifabutin. The result may be subtherapeutic concentrations of the concurrent antiretrovirals and greatly increased concentrations of rifabutin.[25] [26] CDC guidelines recommend specific rifabutin dosing regimens for HIV infected individuals on antiretroviral therapy.[27]

Because rifabutin is metabolized through CYP 3A enzymes, inhibitors of these enzymes, such as fluconazole or clarithromycin, may increase rifabutin plasma concentrations. Because these high plasma levels may increase the risk of adverse reactions, the dosage of rifabutin may need to be reduced.[28]

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Drug and Food Interactions (cont.)

Rifabutin also may decrease the efficacy of oral contraceptives that contain estrogen by inducing the hepatic metabolism of estrogen.[29]

Contraindications

Rifabutin is contraindicated in patients with a history of hypersensitivity to rifabutin or to any of the rifamycins. In addition, rifabutin must not be administered as a single agent for the prevention of MAC infection in patients with active TB because of the likelihood of developing TB that is resistant to both rifabutin and rifampin.[30]

Clinical Trials

For information on clinical trials that involve Rifabutin, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Rifabutin AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[31]

Dosage Form: Capsules containing 150 mg rifabutin.[32]

Storage: Capsules should be stored between 15 C and 30 C (59 F and 86 F) in a tightly closed container.[33]

Chemistry

CAS Name:
(9S,12E,14S,15R,16S,17R,18R,19R,20S,21S,22E,24Z)-6-16,18,20-Tetrahydroxy-1'-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethylspiro(9,4-(epoxypentadeca(1,11,13)trienimino)-2H-furo(2',3':7,8)naphth(1,2-d)imidazole-2,4'-piperidine)-5,10,26(3H,9H-trione,16-acetate[34]

CAS Number: 72559-06-9[35]

Molecular formula: C₄₆H₆₂N₄O₁₁[36]

C65.23%, H7.38%, N6.61%, O20.78%[37]

Molecular weight: 847.02[38]

Physical Description: Rifabutin occurs as a violet-red crystalline powder.[39]

Solubility: Rifabutin is highly soluble in chloroform, soluble in methanol, slightly soluble in ethanol, and minimally soluble in water (0.19 mg/ml).[40]

Other Names

Ansamycin[41]

Ansatiptine[42]

Rifabutina[43]

Rifabutine[44]

Further Reading

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Rifabutin



Manufacturer Information

Rifabutin

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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